The Pharmacological Treatment of Ischemic Stroke goes beyond tPa: Edaravone, an Already Commercialized Promise.

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Introduction

Ischemic stroke is the third leading cause of death in industrialized countries and the most frequent cause of permanent disability in adult worldwide. As expected, disability involves tremendous personal and financial cost to the individual, the family and the health care system.

Objectives

- Make an overview of the main pharmacological treatments for ischemic stroke.
- Provide a general view of the main therapies that are in process of investigation, giving special attention to those that are likely to hit the market in the near future.
- To focus on edaravone, the only free radical scavenger that has provided clinical evidence for therapeutic effects on ischemic stroke.

Methodology

Source:
Data obtained from papers and reviews researched on PubMed database and specialized literature.

Criteria of selection

- Use of key words such as: *ischemic stroke, penumbra, edaravone, pharmacological treatment.*
- Year of publication
- Journal impact factor

Patophisiology and therapeutic targets

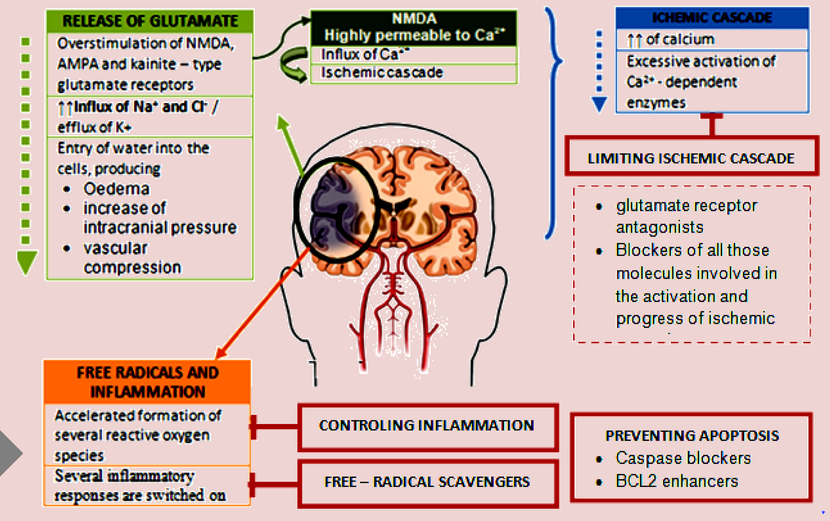
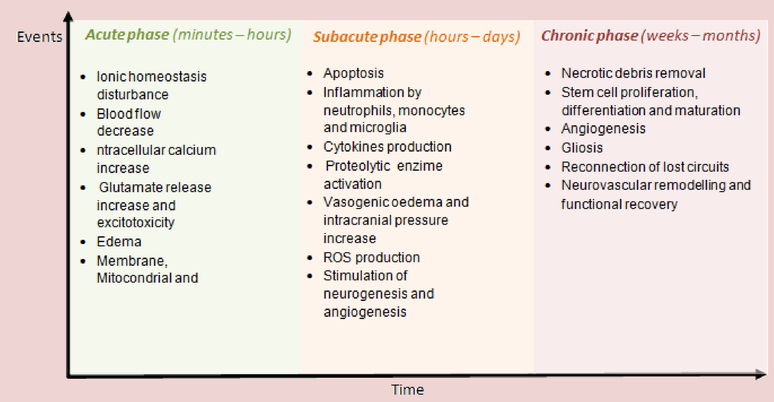
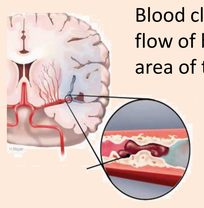


Illustration adapted from WebMD, (2015). Ischemic Stroke. [online] Available at: http://www.webmd.com/stroke/ischemic-stroke [Accessed 25 Mar. 2015].

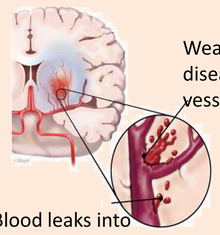


Types of stroke



Blood clot stops the flow of blood to an area of the brain

Ischemic stroke



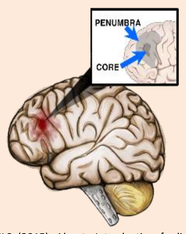
Weakened or diseased blood vessels rupture

Hemorrhagic stroke

Blood leaks into brain tissue

Illustration adapted from Neurowiki2013, (2015). *Alzheimer's Disease and Stroke - Neurowiki*. [online] Available at: http://neurowiki2013.wikidot.com/individual:alzheimers-disease-and-stroke [Accessed 10 May 2015].

Core and penumbra



ASLS, (2015). *About - Introduction*. [online] Available at: http://www.asls.net [Accessed 11 May 2015].

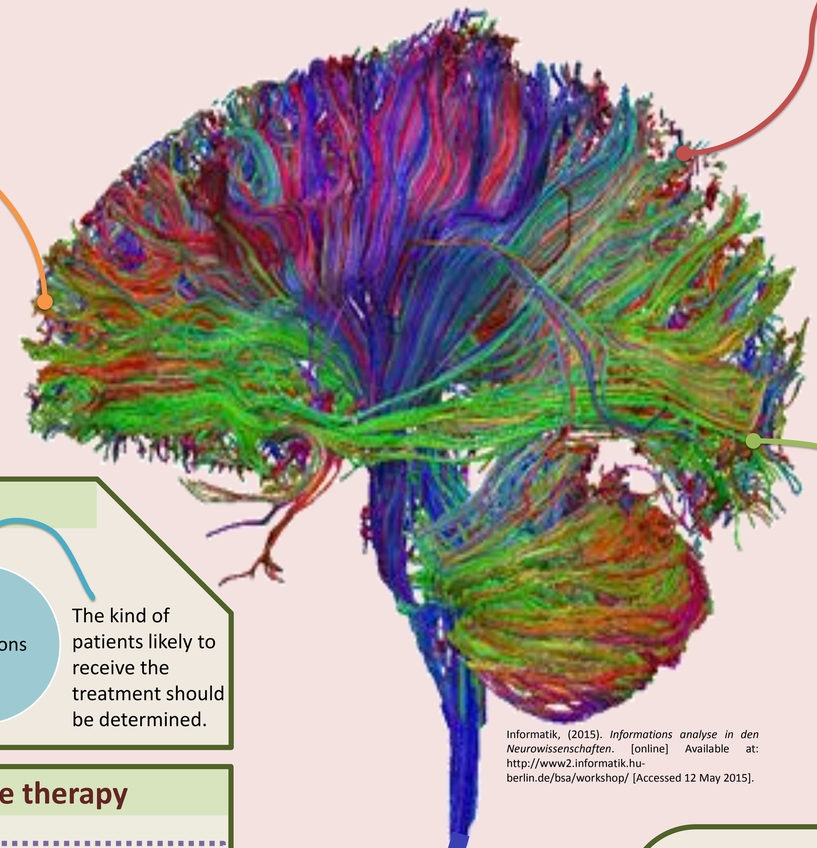
Penumbra	Core
• hypoperfused tissue surrounding the core likely to be salvaged.	• non salvagable tissue

Conventional treatments

Thrombolitic agents: rtPA
- To restore circulation
- It may saves penumbra
- Bleeding complications

Vasodilators
- To prevent secundary ischemia

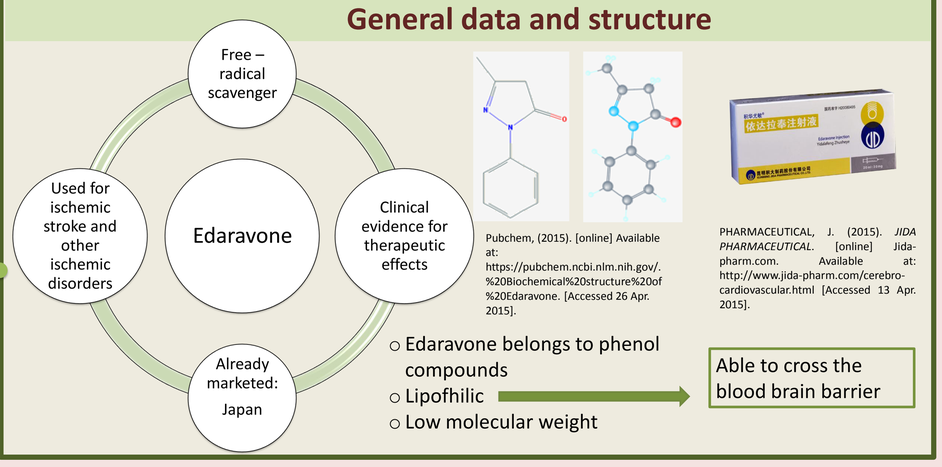
Anticoagulants: Heparine, Aspirine
- To prevent early recurrent stroke
- To improve neurological outcomes
- Bleeding complications



Informatik, (2015). *Informations analyse in den Neurowissenschaften*. [online] Available at: http://www2.informatik.hu-berlin.de/bsa/workshop/ [Accessed 12 May 2015].

EDARAVONE

General data and structure



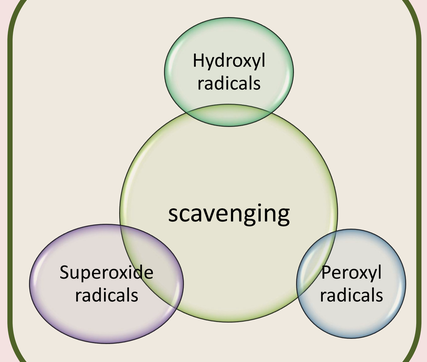
Pubchem, (2015). [online] Available at: https://pubchem.ncbi.nlm.nih.gov/.%20Biochemical%20structure%20of%20Edaravone. [Accessed 26 Apr. 2015].

PHARMACEUTICAL, J. (2015). *JIDA PHARMACEUTICAL*. [online] Jida-pharm.com. Available at: http://www.jida-pharm.com/cerebro-cardiovascular.html [Accessed 13 Apr. 2015].

- Edaravone belongs to phenol compounds
- Lipofhilic
- Low molecular weight

→ Able to cross the blood brain barrier

Mecanism of action



- **Reducing inflammatory response**
- **Protecting ischemic neurons from apoptosis**
- **Inhibiting matrix metalloproteinase - 9**

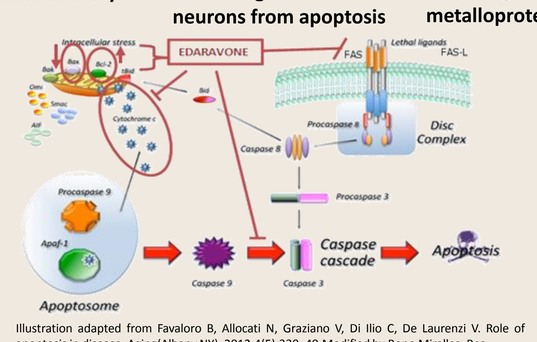
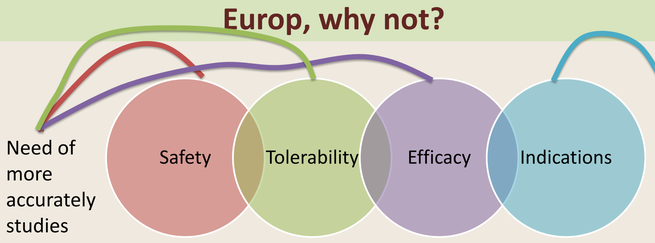


Illustration adapted from Favaloro B, Allocati N, Graziano V, Di Ilio C, De Laurenzi V. Role of apoptosis in disease. Aging(Albany NY). 2012;4(5):330–49.Modified by Bono Miralles, Bea.

Beyond the antioxidant effects…

Europ, why not?



Need of more accurately studies

The kind of patients likely to receive the treatment should be determined.

Synergy of combined tPA – Edaravone therapy

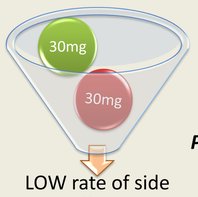
tPA + edaravone

Edaravone strengthen thrombolysis when administrated with tpA, thus increasing benefits of early, but not late, tPA therapy

- Reduced edema
- Less white matter tissue rate
- Inhibition of tPA-induced hemorrhagic transformation
- Less blood-brain barrier damage and oxidative stress

Safety and tolerability

When administrated twice a day in quantities of 30 mg…



Posology

LOW rate of side effects

Some complications can be observed
- Acute renal failure
- Liver dysfunction
- Acute allergic reactions
- CID
- Leukocytopenia
- thrombocytopenia

Efficacy

Under clinical investigation

When administrated within 72 hours….

Reduces infarct volume

Modest improvements in clinical function

Pharmacokinetics

Plasma edaravone concentration seems to disappear without accumulation

Binding rate to serum albumine	• 89 – 91%
Metabolites	• Sulphate complex • Glucoronic acid complex

Conclusions

- 3rd leading cause of death in industralized countries
- Huge repercussion on the individual
- Frequent cause of permanent disability in adult
- Therapeutic options remain limited

It is necessary

The successful treatment of acute ischemic stroke

Research groups working on it

- the amount of potential therapeutic targets is immense.
- many strategies proposed
- necessary to promote research in this field

Thanks to the efforts made by some researches, there are some drugs in a very advanced stage likely to become a reality.